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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/543,033	CAO ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/17/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on July 17, 2009 is acknowledged and has been entered. Claims 1-43 have been canceled. Claims 44-65 have been added. Claims 44-65 are pending.

Claims 44-65 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL to address the new grounds of rejection.

Allowable Subject Matter Withdrawn

The indicated allowability of claim 31 is withdrawn in view of the newly discovered reference(s) to Vagner. Rejections based on the newly cited reference(s) follow as applied to the newly added claims which include the limitation of previous claim 31.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on July 17, 2009 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure

statement is being considered by the examiner. The correction of the references to GenBank entries noted as lacking dates in the submission of November 3, 2006 is acknowledged.

Previous Grounds of Rejection

The rejections over Sequence Compliance have been withdrawn in view of Applicant's amendment to the specification. Further rejections have been withdrawn in view of Applicant's cancellation of the claims.

Claim Interpretation

The term "with specificity" is being given the broadest reasonable interpretation in light of the specification. The term is not explicitly defined in the specification. Instead, the term is referred to in general terms such as "The specificity of a particular compound's effect on untranslated region-dependent expression of one or more other genes (preferably, a plurality of genes) can also be determined utilizing assays well-known to one of skill in the art or described herein" (p. 35, paragraph 254). Therefore, the term is being interpreted as reading on any degree of modulation of expression mediated by the VEGF UTR.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44, 46-47, 49-54, 56, 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyder et al. (Cancer Research. 2000, vol. 60, p. 3183-3190) in view of Vagner et al. (EMBO reports, 2001, 2(10):893-898). Hyder teaches analysis of elements in the 5' and 3' UTR of the VEGF gene which modulate expression.

With regard to claim 44, Hyder teaches a method for identifying a compound that modulates untranslated region (UTR)-dependent expression of human vascular endothelial growth factor (VEGF) protein, said method comprising:

(a) contacting a compound with a human cell engineered to express a reporter protein encoded by a reporter mRNA operably linked to a 5' UTR and a 3' UTR of the human VEGF mRNA (p. 3184, where the human cells were HeLa cells; p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression); and

(b) detecting the level of the reporter protein expressed, wherein an alteration in the level of the reporter protein expressed in the presence of a compound compared to the level of the reporter protein expressed in the absence of the compound or the presence of a negative control indicates that the compound modulates UTR-dependent expression of human VEGF protein (p. 3186, col. 2, where the level of the reporter protein activity is measured in the presence of the 3' UTR, the 5' UTR and without the estrogen compound, See C in Figures 5A and 5B).

With regard to claim 49, Hyder teaches an embodiment of claim 44, wherein the compound does not alter VEGF mRNA levels (p. 3186, col. 2, where the level of the reporter

protein activity is measured in the presence of the 3' UTR, the 5' UTR and without the estrogen compound, See C in Figures 5A and 5B).

With regard to claim 50, Hyder teaches an embodiment of claim 44, wherein the 5' UTR is operably linked upstream of the reporter mRNA encoding the reporter protein (p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression).

With regard to claim 51, Hyder teaches an embodiment of claim 44, wherein the 3' UTR is operably linked downstream of the reporter mRNA encoding the reporter protein (p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression; see Figure 5A, where the 5' and 3' UTR were placed in different orientations).

With regard to claim 52, Hyder teaches an embodiment of claim 44, wherein the reporter protein is firefly luciferase, renilla luciferase, click beetle luciferase, green fluorescent protein, yellow fluorescent protein, red fluorescent protein, cyan fluorescent protein, blue fluorescent protein, beta-galactosidase, beta-glucoronidase, beta-lactamase, chloramphenicol acetyltransferase, or alkaline phosphatase (p. 3184, where the human cells were HeLa cells; p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene).

With regard to claim 53, Hyder teaches an embodiment of claim 44, wherein the human cell is engineered to stably express the reporter protein (p. 3184, where HeLa cells were

transfected with plasmids comprising the UTR regions upstream of the Tk promoter and the luciferase reporter gene and with plasmids expressing ER-alpha or ER-beta).

With regard to claim 54, Hyder teaches an embodiment of claim 44, wherein the human cell is engineered to transiently express the reporter protein (p. 3184, where HeLa cells were transfected with plasmids comprising the UTR regions upstream of the Tk promoter and the luciferase reporter gene and with plasmids expressing ER-alpha or ER-beta).

With regard to claim 56, Hyder teaches an embodiment of claim 44, wherein the human cell is a HeLa cell or a 293 cell (p. 3184, where the human cells were HeLa cells).

With regard to claim 60, Hyder teaches an embodiment of claim 44, 46, 47, wherein the 5' UTR of the human VEGF mRNA is the full-length 5' UTR of human VEGF mRNA and the 3' UTR of the human VEGF mRNA is the full-length 3' UTR of human VEGF mRNA (p. 3184, Figure 1 legend and p. 3187 Figure 5 legend, where the 5' and 3' UTR of VEGF are full-length).

With regard to claim 61, Hyder teaches an embodiment of claim 60, wherein the reporter protein is firefly luciferase, renilla luciferase, click beetle luciferase, green fluorescent protein, yellow fluorescent protein, red fluorescent protein, cyan fluorescent protein, blue fluorescent protein, beta-galactosidase, beta-glucoronidase, beta-lactamase, chloramphenicol acetyltransferase, or alkaline phosphatase (p. 3184, where the human cells were HeLa cells; p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene).

Regarding claim 44, Hyder does not specifically teach that a compound disrupts an interaction between the 5' UTR and the 3' UTR of human VEGF mRNA.

With regard to claims 44, Vagner teaches a disruption of an interaction between the 5' UTR and the 3' UTR of human VEGF mRNA (Figure 1, where the 3' tail/UTR and 5'UTR interact through the translation machinery; this interaction is disrupted or unnecessary in IRES mediated translation).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Hyder to recognize that the estrogen compound may disrupt an interaction between the 3' UTR and 5' UTR of VEGF which occurs in standard translation as taught by Vagner, to arrive at the claimed invention with a reasonable expectation for success. As taught by Vagner, "have adjusted the teachings of Hyder to recognize that the compound disrupts an interaction between the 3' UTR and 5' UTR of VEGF which occurs in standard translation as taught by Vagner, to arrive at the claimed invention with a reasonable expectation for success" (Figure 1 legend, p. 894). As taught by Hyder, "This prompted us to investigate whether the VEGF gene contains sequences that bind the ER and confer hormonal inducibility to reporter constructs in the presence of the two ER subtypes. These studies identified two sequences homologous to the consensus estrogen response element, GGTCAnnnTGACC, which bind both ER-a and ER-b. One of these elements is located in the 5*-untranslated region of the VEGF gene (GGGCAaagTGACT), and the other is located in the 3*-untranslated region (GAGCAcccTGCCC)" (Abstract). Hyder also teaches, "it is a "possibility that estrogens may also regulate VEGF via other mechanisms, e.g., by protein-protein interactions, via kinase-mediated pathways, or by binding to one ERE half-site followed by cooperation with other transcription sites (51–53)." (p. 3189, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have

adjusted the teachings of Hyder to recognize that the compound disrupts an interaction between the 3' UTR and 5' UTR of VEGF which occurs in standard translation as taught by Vagner, to arrive at the claimed invention with a reasonable expectation for success.

Claims 45, 49-54, 56 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyder et al. (Cancer Research. 2000, vol. 60, p. 3183-3190) in view of Vagner et al. (EMBO reports, 2001, 2(10):893-898) as applied to claims 44, 46-47, 49-54, 56, 60-61 above and further in view of Levy et al. (Journal of Biological Chemistry, 1998, vol. 273, no. 11, p. 6417-6423). Hyder teaches analysis of elements in the 5' and 3' UTR of the VEGF gene which modulate expression.

With regard to claim 45, teaches a method for identifying a compound that modulates UTR-dependent expression of human VEGF protein said method comprising:
(a) contacting a compound with mixture expressing a reporter protein encoded by a reporter mRNA operably linked to a 5' UTR and a 3' UTR of the human VEGF mRNA (p. 3184, where the human cells were HeLa cells; p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression); and
(b) detecting the level of the reporter protein expressed, wherein an alteration in the level of the reporter protein expressed in the presence of a compound compared to the level of the reporter protein expressed in the absence of the compound or the presence of a negative control indicates that the compound modulates UTR-dependent expression of human VEGF protein (p. 3186, col.

2, where the level of the reporter protein activity is measured in the presence of the 3' UTR, the 5' UTR and without the estrogen compound, See C in Figures 5A and 5B).

With regard to claim 49, Hyder teaches an embodiment of claim 45, wherein the compound does not alter VEGF mRNA levels (p. 3186, col. 2, where the level of the reporter protein activity is measured in the presence of the 3' UTR, the 5' UTR and without the estrogen compound, See C in Figures 5A and 5B).

With regard to claim 50, Hyder teaches an embodiment of claim 45, wherein the 5' UTR is operably linked upstream of the reporter mRNA encoding the reporter protein (p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression; see Figure 5A, where the 5' and 3' UTR were placed in different orientations).

With regard to claim 51, Hyder teaches an embodiment of claim 45, wherein the 3' UTR is operably linked downstream of the reporter mRNA encoding the reporter protein (p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression; see Figure 5A, where the 5' and 3' UTR were placed in different orientations).

With regard to claim 52, Hyder teaches an embodiment of claim 45, wherein the reporter protein is firefly luciferase, renilla luciferase, click beetle luciferase, green fluorescent protein, yellow fluorescent protein, red fluorescent protein, cyan fluorescent protein, blue fluorescent protein, beta-galactosidase, beta-glucoronidase, beta-lactamase, chloramphenicol acetyltransferase, or alkaline phosphatase (p. 3184, where the human cells were HeLa cells; p.

3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene).

With regard to claim 53, Hyder teaches an embodiment of claim 45, wherein the human cell is engineered to stably express the reporter protein (p. 3184, where HeLa cells were transfected with plasmids comprising the UTR regions upstream of the Tk promoter and the luciferase reporter gene and with plasmids expressing ER-alpha or ER-beta).

With regard to claim 54, Hyder teaches an embodiment of claim 45, wherein the human cell is engineered to transiently express the reporter protein (p. 3184, where HeLa cells were transfected with plasmids comprising the UTR regions upstream of the Tk promoter and the luciferase reporter gene and with plasmids expressing ER-alpha or ER-beta).

With regard to claim 56, Hyder teaches an embodiment of claim 45, wherein the human cell is a HeLa cell or a 293 cell (p. 3184, where the human cells were HeLa cells).

With regard to claim 60, Hyder teaches an embodiment of claim 45, 48, wherein the 5' UTR of the human VEGF mRNA is the full-length 5' UTR of human VEGF mRNA and the 3' UTR of the human VEGF mRNA is the full-length 3' UTR of human VEGF mRNA (p. 3184, Figure 1 legend and p. 3187 Figure 5 legend, where the 5' and 3' UTR of VEGF are full-length).

Regarding claim 45, Hyder does not teach contacting the cell with a cell-free translation mixture and Hyder does not teach that a compound disrupts an interaction between the 5' UTR and the 3' UTR of human VEGF mRNA. Regarding claim 55, Hyder does not specifically teach a step of measuring the effect of the compound on the expression of human VEGF.

With regard to claim 45, Levy teaches contacting the cell with a cell-free translation mixture (p. 6418, col. 2, where cell free extracts from 293T clones were analyzed with HuR affinity purified antiserum).

With regard to claim 55, Levy teaches an embodiment of claim 45, further comprising measuring the effect of the compound on the level of expression of the human VEGF protein (Figure 5 and 6, where the Western blot shows expression analysis of the VEGF gene).

With regard to claim 57, Levy teaches an embodiment of claim 45, wherein the cell-free translation mixture is a cell extract derived from a human cell, a yeast cell, a mouse cell, a rat cell, a Chinese hamster ovary ("CHO") cell, a Xenopus oocyte, a primary cell, an undifferentiated cancer cell, or a rye embryo (p. 6418, col. 2, where cell free extracts from 293T clones were analyzed with HuR affinity purified antiserum and where 293T is a human cell).

Regarding claim 45, neither Hyder or Levy specifically teach that a compound disrupts an interaction between the 5' UTR and the 3' UTR of human VEGF mRNA.

With regard to claims 45, Vagner teaches a disruption of an interaction between the 5' UTR and the 3' UTR of human VEGF mRNA (Figure 1, where the 3' tail/UTR and 5'UTR interact through the translation machinery; this interaction is disrupted or unnecessary in IRES mediated translation).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Hyder and Levy to recognize that the estrogen compound may disrupt an interaction between the 3' UTR and 5' UTR of VEGF which occurs in standard translation as taught by Vagner, to arrive at the claimed invention with a reasonable expectation for success. As taught by Vagner, "have adjusted the teachings of Hyder

to recognize that the compound disrupts an interaction between the 3' UTR and 5' UTR of VEGF which occurs in standard translation as taught by Vagner, to arrive at the claimed invention with a reasonable expectation for success" (Figure 1 legend, p. 894). As taught by Hyder, "This prompted us to investigate whether the VEGF gene contains sequences that bind the ER and confer hormonal inducibility to reporter constructs in the presence of the two ER subtypes. These studies identified two sequences homologous to the consensus estrogen response element, GGTCAnnnTGACC, which bind both ER-a and ER-b. One of these elements is located in the 5*-untranslated region of the VEGF gene (GGGCAaagTGACT), and the other is located in the 3*-untranslated region (GAGCAcccTGCCC)" (Abstract). Hyder also teaches, "it is a "possibility that estrogens may also regulate VEGF via other mechanisms, e.g., by protein-protein interactions, via kinase-mediated pathways, or by binding to one ERE half-site followed by cooperation with other transcription sites (51–53)." (p. 3189, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Hyder and Levy to recognize that the compound disrupts an interaction between the 3' UTR and 5' UTR of VEGF which occurs in standard translation as taught by Vagner, to arrive at the claimed invention with a reasonable expectation for success.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the additional VEGF targets to the reporter gene construct format described by Hyder. Levy teaches an analysis of the hypoxic stabilization of VEGF in the presence of an RNA binding protein, HuR, however, the inclusion of this format in the analysis of the control of the hypoxic stabilization, including the analysis of binding sites for the HuR protein would mesh well with the techniques described generally by Hyder.

Claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyder et al. (Cancer Research. 2000, vol. 60, p. 3183-3190) in view of Vagner et al. (EMBO reports, 2001, 2(10):893-898) as applied to claims 44, 46-47, 49-54, 56, 60-61 above and further in view of Stein et al. (Molec. Cell Biol., 1998, 18(6):3112-3119). Hyder teaches analysis of elements in the 5' and 3' UTR of the VEGF gene which modulate expression.

With regard to claim 46, Hyder teaches a method for identifying a compound that specifically modulates UTR-dependent expression of human VEGF protein said method comprising:

(a) contacting a compound with a first human cell engineered to express a first reporter protein encoded by a first reporter mRNA operably linked to a 5' UTR and a 3' UTR of the human VEGF mRNA (p. 3184, where the human cells were HeLa cells; p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression); and

(c) detecting the level of expression of the first reporter protein (p. 3186, col. 2, where the level of the reporter protein activity is measured in the presence of the 3' UTR, the 5' UTR and without the estrogen compound, See C in Figures 5A and 5B).

With regard to claim 47, Hyder teaches a method for identifying a compound that specifically modulates UTR-dependent expression of human VEGF protein said method comprising:

(a) contacting a compound with a first human cell engineered to express a first reporter protein encoded by a first reporter mRNA operably linked to a 5' UTR and a 3' UTR of the human

VEGF mRNA (p. 3184, where the human cells were HeLa cells; p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression); and (c) detecting the level of expression of the first reporter protein, wherein a compound that specifically modulates UTR-dependent expression of human VEGF protein is identified if the level of expression of the first reporter protein by the first human cell in the presence of the compound is altered relative to the level of expression of the first reporter protein by the first human cell in the absence of the compound or the presence of a negative control (p. 3186, col. 2, where the level of the reporter protein activity is measured in the presence of the 3' UTR, the 5' UTR and without the estrogen compound, See C in Figures 5A and 5B).

Regarding claims 46-47, Hyder does not teach the step of comparing the VEGF 5' UTR to another mRNA with a 5' and 3' UTR. Regarding claim 46-47, Hyder does not specifically teach that a compound disrupts an interaction between the 5' UTR and the 3' UTR of human VEGF mRNA or the second molecule.

With regard to claims 46-47, Vagner teaches a compound disrupts an interaction between the 5' UTR and the 3' UTR of human VEGF mRNA (Figure 1, where the 3' tail/UTR and 5'UTR interact through the translation machinery; this interaction is disrupted in IRES mediated translation).

With regard to claim 46-47, Stein teaches (b) contacting the compound with a panel of human cells, wherein each human cell in the panel is isolated from each other and each human cell is engineered to express a reporter protein encoded by a reporter mRNA operably linked to a 5' UTR and a 3' UTR of a mRNA other than the human VEGF mRNA (p. 3115, Figure 3, where

the reporter was operably linked to UTR of BiP mRNA instead of VEGF) and (c) detecting the level of expression of either the second reporter protein (p. 3115, Figure 3, where the levels of LUC or SeAP were measured with VEGF UTR construct and compared to constructs including the BiP UTRs in either hypoxic or non-hypoxic conditions), and the level of expression of each isolated reporter protein in the panel in the presence of the compound is not altered or not substantially altered relative to the level of expression of each isolated reporter protein in the panel in the absence of the compound or the presence of a negative control (p. 3115, Figure 3, where the levels of LUC or SeAP were measured with VEGF UTR construct and compared to constructs including the BiP UTRs in either hypoxic or non-hypoxic conditions).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Hyder and Vagner to include the step of including an additional control, including the 5' and 3' UTR regulatory regions from a different gene as taught by Stein to arrive at the claimed invention with a reasonable expectation for success. As taught by Stein, "a comparison was made with the well-characterized cellular IRES contained in the 5'UTR of BiP mRNA (24)." and Stein notes "As shown in Fig. 3B, the VEGF IRES was fivefold more efficient than the BiP IRES in directing SeAP production". Stein also teaches the analysis of the reporter levels in hypoxic and non-hypoxic conditions. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Hyder and Vagner to include the step of including an additional control, including the 5' and 3' UTR regulatory regions from a different gene as taught by Stein to arrive at the claimed invention with a reasonable expectation for success.

Claims 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hyder et al. (Cancer Research. 2000, vol. 60, p. 3183-3190) in view of Vagner et al. (EMBO reports, 2001, 2(10):893-898) and Levy et al. (Journal of Biological Chemistry, 1998, vol. 273, no. 11, p. 6417-6423) as applied to claims 45, 49-54, 56 and 60 above and further in view of Stein et al. (Molec. Cell Biol., 1998, 18(6):3112-3119). Hyder teaches analysis of elements in the 5' and 3' UTR of the VEGF gene which modulate expression.

With regard to claim 48, Hyder teaches a method for identifying a compound that specifically modulates UTR-dependent expression of human VEGF protein said method comprising:

(a) contacting a compound with a cell-free translation mixture expressing a first reporter protein encoded by a first reporter mRNA operably linked to a 5' UTR and a 3' UTR of the human VEGF mRNA (p. 3184, where the human cells were HeLa cells; p. 3185, col. 2, where tandem copies of the 5' and 3' UTR upstream of a promoter linked to a luciferase reporter gene and the cell was contacted with ER-alpha or ER-beta and detected reporter gene expression);

(c) detecting the level of expression of the first reporter proteins, wherein a compound that specifically modulates UTR-dependent expression of the human VEGF protein is identified if the level of expression of the first reporter protein in the presence of the compound is altered relative to the level of expression of the first reporter protein in the absence of the compound or the presence of a negative control (p. 3186, col. 2, where the level of the reporter protein activity is measured in the presence of the 3' UTR, the 5' UTR and without the estrogen compound, See C in Figures 5A and 5B).

Regarding claim 48, neither Hyder nor Levy teach (b) contacting the compound with a translation mixture expressing a second reporter protein encoded by a second reporter mRNA operably linked to a 5' UTR and a 3' UTR of a mRNA other than the human VEGF mRNA; and (c) detecting the level of expression of the second reporter proteins, and the level of expression of the second reporter protein in the presence of the compound is not altered or not substantially altered relative to the level of expression of the second reporter protein in the absence of the compound or the presence of a negative control.

With regard to claim 48, Stein teaches a method comprising (b) contacting the compound with a translation mixture expressing a second reporter protein encoded by a second reporter mRNA operably linked to a 5' UTR and a 3' UTR of a mRNA other than the human VEGF mRNA (p. 3115, Figure 3, where the reporter was operably linked to UTR of BiP mRNA instead of VEGF); and

(c) detecting the level of expression of the second reporter proteins, and the level of expression of the second reporter protein in the presence of the compound is not altered or not substantially altered relative to the level of expression of the second reporter protein in the absence of the compound or the presence of a negative control (p. 3115, Figure 3, where the levels of LUC or SeAP were measured with VEGF UTR construct and compared to constructs including the BiP UTRs in either hypoxic or non-hypoxic conditions).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Hyder, Vagner and Levy to include the step of including an additional control, including the 5' and 3' UTR regulatory regions from a different gene as taught by Stein to arrive at the claimed invention with a reasonable expectation

for success. As taught by Stein, "a comparison was made with the well-characterized cellular IRES contained in the 5'UTR of BiP mRNA (24)." and Stein notes "As shown in Fig. 3B, the VEGF IRES was fivefold more efficient than the BiP IRES in directing SeAP production". Stein also teaches the analysis of the reporter levels in hypoxic and non-hypoxic conditions. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Hyder, Vagner and Levy to include the step of including an additional control, including the 5' and 3' UTR regulatory regions from a different gene as taught by Stein to arrive at the claimed invention with a reasonable expectation for success.

Claims 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyder et al. (Cancer Research. 2000, vol. 60, p. 3183-3190) in view of Vagner et al. (EMBO reports, 2001, 2(10):893-898) and Levy et al. (Journal of Biological Chemistry, 1998, vol. 273, no. 11, p. 6417-6423) as applied to claims 45, 49-54, 56 and 60 above and further in view of Claffey et al. (Mol. Biol. Cell, 1998, 9(2):469-81). Hyder teaches analysis of elements in the 5' and 3' UTR of the VEGF gene which modulate expression.

With regard to claim 58, Claffey teaches an embodiment of claim 44, 45, 46, 47 or 48, wherein the 5' UTR of the human VEGF mRNA is encoded by a nucleotide sequence comprising SEQ ID NO: 17 (see alignment below, where the VEGF sequence of Claffey comprises the 5' UTR of VEGF mRNA of SEQ ID NO:17).

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Qy          1 AAGAGCTCCAGAGAGAAGTCGAGGAAGAGAGAGACGGGGTCAGAGAGAGCGCGCGGGCGT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 AAGAGCTCCAGAGAGAAGTCGAGGAAGAGAGAGACGGGGTCAGAGAGAGCGCGCGGGCGT 60

Qy         61 GCGAGCAGCGAAAGCGACAGGGGCAAAGTGAGTGACCTGCTTTTGGGGGTGACCGCCGGA 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GCGAGCAGCGAAAGCGACAGGGGCAAAGTGAGTGACCTGCTTTTGGGGGTGACCGCCGGA 120
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Qy        121 GCGCGGCGTGAGCCCTCCCCCTTGGGATCCCGCAGCTGACCAGTCGCGCTGACGGACAGA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GCGCGGCGTGAGCCCTCCCCCTTGGGATCCCGCAGCTGACCAGTCGCGCTGACGGACAGA 180

Qy        181 CAGACAGACACCGCCCCCAGCCCCAGTTACCACCTCCTCCCCGGCCGGCGGCGGACAGTG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 CAGACAGACACCGCCCCCAGCCCCAGTTACCACCTCCTCCCCGGCCGGCGGCGGACAGTG 240

Qy        241 GACGCGGCGGCGAGCCGCGGGCAGGGGCCGGAGCCCGCCCCCGGAGGCGGGGTGGAGGGG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 GACGCGGCGGCGAGCCGCGGGCAGGGGCCGGAGCCCGCCCCCGGAGGCGGGGTGGAGGGG 300

Qy        301 GTCGGAGCTCGCGGCGTCGCACTGAAACTTTTCGTCCAACTTCTGGGCTGTTCTCGCTTC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 GTCGGAGCTCGCGGCGTCGCACTGAAACTTTTCGTCCAACTTCTGGGCTGTTCTCGCTTC 360

Qy        361 GGAGGAGCCGTGGTCCGCGCGGGGGAAGCCGAGCCGAGCGGAGCCGCGAGAAGTGCTAGC 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 GGAGGAGCCGTGGTCCGCGCGGGGGAAGCCGAGCCGAGCGGAGCCGCGAGAAGTGCTAGC 420

Qy        421 TCGGGCCGGGAGGAGCCGCAGCCGGAGGAGGGGGAGGAGGAAGAAGAGAAGGAAGAGGAG 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 TCGGGCCGGGAGGAGCCGCAGCCGGAGGAGGGGGAGGAGGAAGAAGAGAAGGAAGAGGAG 480

Qy        481 AGGGGGCCGCAGTGGCGACTCGGCGCTCGGAAGCCGGGCTCATGGACGGGTGAGGCGGCG 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 AGGGGGCCGCAGTGGCGACTCGGCGCTCGGAAGCCGGGCTCATGGACGGGTGAGGCGGCG 540

Qy        541 GTGTGCGCAGACAGTGCTCCAGCGCGCGCGCTCCCCAGCCCTGGCCCGGCCTCGGGCCGG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 GTGTGCGCAGACAGTGCTCCAGCGCGCGCGCTCCCCAGCCCTGGCCCGGCCTCGGGCCGG 600

Qy        601 GAGGAAGAGTAGCTCGCCGAGGCGCCGAGGAGAGCGGGCCGCCCCACAGCCCGAGCCGGA 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 GAGGAAGAGTAGCTCGCCGAGGCGCCGAGGAGAGCGGGCCGCCCCACAGCCCGAGCCGGA 660

Qy        661 GAGGGACGCGAGCCGCGCGCCCCGGTCGGGCCTCCGAAACC 701
              |||||||||||||||||||||||||||||||||||||||||
Db        661 GAGGGACGCGAGCCGCGCGCCCCGGTCGGGCCTCCGAAACC 701
```

With regard to claim 59, Claffey teaches an embodiment of claim 44, 45, 46, 47 or 48, wherein the 3' UTR of the human VEGF mRNA is encoded by a nucleotide sequence comprising SEQ ID NO: 18 (see alignment below, where the VEGF sequence of Claffey comprises the 3' UTR of VEGF mRNA of SEQ ID NO:18).

```
Qy          1 TGAGCCGGGCAGGAGGAAGGAGCCTCCCTCAGGGTTTCGGGAACCAGATCTCTCTCCAGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1275 TGAGCCGGGCAGGAGGAAGGAGCCTCCCTCAGGGTTTCGGGAACCAGATCTCTCTCCAGG 1334

Qy         61 AAAGACTGATACAGAACGATCGATACAGAAACCACGCTGCCGCCACCACACCATCACCAT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1335 AAAGACTGATACAGAACGATCGATACAGAAACCACGCTGCCGCCACCACACCATCACCAT 1394

Qy        121 CGACAGAACAGTCCTTAATCCAGAAACCTGAAATGAAGGAAGAGGAGACTCTGCGCAGAG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1395 CGACAGAACAGTCCTTAATCCAGAAACCTGAAATGAAGGAAGAGGAGACTCTGCGCAGAG 1454

Qy        181 CACTTTGGGTCCGGAGGGCGAGACTCCGGCGGAAGCATTCCCGGGCGGGTGACCCAGCAC 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1455 CACTTTGGGTCCGGAGGGCGAGACTCCGGCGGAAGCATTCCCGGGCGGGTGACCCAGCAC 1514

Qy        241 GGTCCCTCTTGGAATTGGATTCGCCATTTTATTTTTCTTGCTGCTAAATCACCGAGCCCG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1515 GGTCCCTCTTGGAATTGGATTCGCCATTTTATTTTTCTTGCTGCTAAATCACCGAGCCCG 1574

Qy        301 GAAGATTAGAGAGTTTTATTTCTGGGATTCCTGTAGACACACCCACCCACATACATACAT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1575 GAAGATTAGAGAGTTTTATTTCTGGGATTCCTGTAGACACACCCACCCACATACATACAT 1634

Qy        361 TTATATATATATATATTATATATATATAAAAATAAATATCTCTATTTTATATATATAAAA 420
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                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1635 TTATATATATATATATTATATATATATAAAAATAAATATCTCTATTTTATATATATAAAA 1694

Qy        421 TATATATATTCTTTTTTTAAATTAACAGTGCTAATGTTATTGGTGTCTTCACTGGATGTA 480
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1695 TATATATATTCTTTTTTTAAATTAACAGTGCTAATGTTATTGGTGTCTTCACTGGATGTA 1754

Qy        481 TTTGACTGCTGTGGACTTGAGTTGGGAGGGGAATGTTCCCACTCAGATCCTGACAGGGAA 540
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1755 TTTGACTGCTGTGGACTTGAGTTGGGAGGGGAATGTTCCCACTCAGATCCTGACAGGGAA 1814

Qy        541 GAGGAGGAGATGAGAGACTCTGGCATGATCTTTTTTTTGTCCCACTTGGTGGGGCCAGGG 600
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1815 GAGGAGGAGATGAGAGACTCTGGCATGATCTTTTTTTTGTCCCACTTGGTGGGGCCAGGG 1874

Qy        601 TCCTCTCCCCTGCCCAAGAATGTGCAAGGCCAGGGCATGGGGGCAAATATGACCCAGTTT 660
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1875 TCCTCTCCCCTGCCCAAGAATGTGCAAGGCCAGGGCATGGGGGCAAATATGACCCAGTTT 1934

Qy        661 TGGGAACACCGACAAACCCAGCCCTGGCGCTGAGCCTCTCTACCCCAGGTCAGACGGACA 720
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1935 TGGGAACACCGACAAACCCAGCCCTGGCGCTGAGCCTCTCTACCCCAGGTCAGACGGACA 1994

Qy        721 GAAAGACAAATCACAGGTTCCGGGATGAGGACACCGGCTCTGACCAGGAGTTTGGGGAGC 780
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1995 GAAAGACAAATCACAGGTTCCGGGATGAGGACACCGGCTCTGACCAGGAGTTTGGGGAGC 2054

Qy        781 TTCAGGACATTGCTGTGCTTTGGGGATTCCCTCCACATGCTGCACGCGCATCTCGCCCCC 840
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2055 TTCAGGACATTGCTGTGCTTTGGGGATTCCCTCCACATGCTGCACGCGCATCTCGCCCCC 2114

Qy        841 AGGGGCACTGCCTGGAAGATTCAGGAGCCTGGGCGGCCTTCGCTTACTCTCACCTGCTTC 900
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2115 AGGGGCACTGCCTGGAAGATTCAGGAGCCTGGGCGGCCTTCGCTTACTCTCACCTGCTTC 2174

Qy        901 TGAGTTGCCCAGGAGGCCACTGGCAGATGTCCCGGCGAAGAGAAGAGACACATTGTTGGA 960
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2175 TGAGTTGCCCAGGAGGCCACTGGCAGATGTCCCGGCGAAGAGAAGAGACACATTGTTGGA 2234

Qy        961 AGAAGCAGCCCATGACAGCGCCCCTTCCTGGGACTCGCCCTCATCCTCTTCCTGCTCCCC 1020
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2235 AGAAGCAGCCCATGACAGCGCCCCTTCCTGGGACTCGCCCTCATCCTCTTCCTGCTCCCC 2294

Qy       1021 TTCCTGGGGTGCAGCCTAAAAGGACCTATGTCCTCACACCATTGAAACCACTAGTTCTGT 1080
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2295 TTCCTGGGGTGCAGCCTAAAAGGACCTATGTCCTCACACCATTGAAACCACTAGTTCTGT 2354

Qy       1081 CCCCCCAGGAAACCTGGTTGTGTGTGTGTGAGTGGTTGACCTTCCTCCATCCCCTGGTCC 1140
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2355 CCCCCCAGGAAACCTGGTTGTGTGTGTGTGAGTGGTTGACCTTCCTCCATCCCCTGGTCC 2414

Qy       1141 TTCCCTTCCCTTCCCGAGGCACAGAGAGACAGGGCAGGATCCACGTGCCCATTGTGGAGG 1200
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2415 TTCCCTTCCCTTCCCGAGGCACAGAGAGACAGGGCAGGATCCACGTGCCCATTGTGGAGG 2474

Qy       1201 CAGAGAAAAGAGAAAGTGTTTTATATACGGTACTTATTTAATATCCCTTTTTAATTAGAA 1260
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2475 CAGAGAAAAGAGAAAGTGTTTTATATACGGTACTTATTTAATATCCCTTTTTAATTAGAA 2534

Qy       1261 ATTAGAACAGTTAATTTAATTAAAGAGTAGGGTTTTTTTTCAGTATTCTTGGTTAATATT 1320
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2535 ATTAGAACAGTTAATTTAATTAAAGAGTAGGGTTTTTTTTCAGTATTCTTGGTTAATATT 2594

Qy       1321 TAATTTCAACTATTTATGAGATGTATCTTTTGCTCTCTCTTGCTCTCTTATTTGTACCGG 1380
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2595 TAATTTCAACTATTTATGAGATGTATCTTTTGCTCTCTCTTGCTCTCTTATTTGTACCGG 2654

Qy       1381 TTTTTGTATATAAAATTCATGTTTCCAATCTCTCTCTCCCTGATCGGTGACAGTCACTAG 1440
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2655 TTTTTGTATATAAAATTCATGTTTCCAATCTCTCTCTCCCTGATCGGTGACAGTCACTAG 2714

Qy       1441 CTTATCTTGAACAGATATTTAATTTTGCTAACACTCAGCTCTGCCCTCCCCGATCCCCTG 1500
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2715 CTTATCTTGAACAGATATTTAATTTTGCTAACACTCAGCTCTGCCCTCCCCGATCCCCTG 2774

Qy       1501 GCTCCCCAGCACACATTCCTTTGAAAGAGGGTTTCAATATACATCTACATACTATATATA 1560
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2775 GCTCCCCAGCACACATTCCTTTGAAAGAGGGTTTCAATATACATCTACATACTATATATA 2834

Qy       1561 TATTGGGCAACTTGTATTTGTGTGTATATATATATATATATGTTTATGTATATATGTGAT 1620
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2835 TATTGGGCAACTTGTATTTGTGTGTATATATATATATATATGTTTATGTATATATGTGAT 2894
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Qy       1621 CCTGAAAAAATAAACATCGCTATTCTGTTTTTTATATGTTCAAACCAAACAAGAAAAAAT 1680
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2895 CCTGAAAAAATAAACATCGCTATTCTGTTTTTTATATGTTCAAACCAAACAAGAAAAAAT 2954

Qy       1681 AGAGAATTCTACATACTAAATCTCTCTCCTTTTTTAATTTTAATATTTGTTATCATTTAT 1740
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2955 AGAGAATTCTACATACTAAATCTCTCTCCTTTTTTAATTTTAATATTTGTTATCATTTAT 3014

Qy       1741 TTATTGGTGCTACTGTTTATCCGTAATAATTGTGGGGAAAAGATATTAACATCACGTCTT 1800
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3015 TTATTGGTGCTACTGTTTATCCGTAATAATTGTGGGGAAAAGATATTAACATCACGTCTT 3074

Qy       1801 TGTCTCTAGTGCAGTTTTTCGAGATATTCCGTAGTACATATTTATTTTTAAACAACGACA 1860
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3075 TGTCTCTAGTGCAGTTTTTCGAGATATTCCGTAGTACATATTTATTTTTAAACAACGACA 3134

Qy       1861 AAGAAATACAGATATATCTTAAAAAAAAAAAA 1892
              ||||||||||||||||||||||||||||||||
Db       3135 AAGAAATACAGATATATCTTAAAAAAAAAAAA 3166
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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Hyder, Levy and Vagner to include the specific 5' UTR sequence and 3' UTR sequence of Claffey to arrive at the claimed invention with a reasonable expectation for success. Claffey teaches the sequences of the 5' and 3' UTR of VEGF, as also generally taught by Hyder, Levy and Vagner. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Hyder, Levy and Vagner to include the specific 5' UTR sequence and 3' UTR sequence of Claffey to arrive at the claimed invention with a reasonable expectation for success.

Claims 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyder et al. (Cancer Research. 2000, vol. 60, p. 3183-3190) in view of Vagner et al. (EMBO reports, 2001, 2(10):893-898) and Levy et al. (Journal of Biological Chemistry, 1998, vol. 273, no. 11, p. 6417-6423) as applied to claims 45, 49-54, 56 and 60 above and further in view of Cho et al. (Expert Opin Ther Targets, 2002, vol. 6, no. 6, p. 679-689). Hyder teaches analysis of elements in the 5' and 3' UTR of the VEGF gene which modulate expression.

With regard to claim 64-65, Hyder teaches an embodiment of claim 44 or 45, wherein the alteration in the level of the reporter protein expressed is detected by measuring the activity of the reporter protein.

Regarding claims 62-63, Hyder does not teach determining the structure of the compound.

With regard to claim 62, Cho teaches an embodiment of claim 44 or 45 further comprising (c) determining the structure of the compound (Figure 8, where in a library where the small molecule comprises a protein, the structure can be determined using mass spectrometry).

With regard to claim 63, Cho teaches an embodiment of claim 62, wherein the structure of the compound is determined by mass spectroscopy, NMR, vibrational spectroscopy, or X-ray crystallography (Figure 8, where in a library where the small molecule comprises a protein, the structure can be determined using mass spectrometry).

It would have been prima facie obvious to one of ordinary skill to include a rationally designed target library in the screening for compounds which modulate expression of VEGF, particularly as controlled or mediated by the 5' or 3' UTR of the VEGF gene. Cho teaches "proteomics analyzes differentially regulated proteins, elucidates protein structure and function, and indentifies interacting partners" (p. 684). Cho also teaches "the most common method in proteome analysis is to perform a 2D gel electrophoresis (2-DE) on a protein sample preparation isolated from a defined set of conditions (i.e. normal versus diseased and control versus drug-treated). Protein bands of interest are digested and identified using mass spectrometry (See Figure 8)" (p. 686). Therefore, it would have been obvious to one of ordinary skill to include a

rationally designed target library in the screening for compounds which modulate expression of VEGF, particularly as controlled or mediated by the 5' or 3' UTR of the VEGF gene.

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Examiner, Art Unit 1637

SKM